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Pharmacogenomics for sustainable drug development: A narrative review of precision medicine, green chemistry, and multi-omics innovation

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ABSTRACT

Pharmacogenomics (PGx) is the study of how genetic differences affect how people react to medications. It is an important aspect of improving personalized treatment. Russo claimed that PGx can make treatments more effective and reduce adverse drug reactions (ADRs) by matching them to your genetic profile. This is a major step up from the old "one-size-fits-all" way of doing things. This review talks about how PGx helps make pharmaceuticals that are better for the environment. It talks about how PGx can help with dosing, figuring out how medications will act, and preventing ADRs. All of these things contribute to better and cheaper healthcare. PGx has a lot of potential, but there are a number of drawbacks that make it impossible for many individuals to use it. Some of these are that genomic databases do not have enough variety, gene–drug interaction models are too simplistic, and it is hard to get people to accept them in clinical settings since there is not enough infrastructure or training. Ethical and regulatory difficulties, notably those about protecting data and getting access to genetic testing, make it even tougher to put into action. It is also hard to use PGx in regions with low resources because it costs so much. This review reveals how PGx could help save healthcare expenditures, reduce ADRs, and make it less likely that clinical trials would fail. It also talks about crucial strategies to get over current problems, such as making genetic studies more varied, enhancing clinical integration, and dealing with financial challenges. By looking at PGx from several angles, this study hopes to improve research, change policy, and promote a broader and fairer use of PGx in clinical practice.

1. INTRODUCTION

Pharmacogenomics (PGx), the investigation of how genetic differences influence drug response, is a key driver of personalized medicine and sustainable drug development. PGx makes it feasible to customize treatments for each person by looking at how single genes or groups of genes affect how well drugs work and how harmful they are. This tailored method maximizes the effectiveness of treatment while minimizing the

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risk of adverse drug reactions (ADRs). It moves away from the long-standing "one-size-fits-all" approach to treatment [1]. One of the key objectives of PGx is to create low-cost and widely available genetic testing tools that support clinicians in the prediction of drug response, dosage adjustment, and reduction of undesirable side effects. This level of accuracy not only makes patients safer, but it also cuts down on the time and money spent on trial-and-error prescribing, which helps healthcare systems stay in business [2]. There are over 3 billion base pairs in the human genome, and single-nucleotide polymorphisms (SNPs) happen every 1,000 bases. These genetic variations have a strong impact on drug metabolism, immune function, DNA repair, and disease progression. For instance, oncogenes and tumor suppressor gene variation influence cancer treatment efficacy, highlighting the clinical importance of PGx [3]. Incorporation of PGx into drug development pipelines is likely to minimize clinical trial failures, maximize drug use, and reduce healthcare expenditures. PGx not only improves patient outcomes by increasing efficacy and minimizing ADRs through customized therapies, but it also helps create medication strategies that are more successful, cost-efficient, and long-lasting [4].

2. METHODOLOGY

This article uses a narrative review style to bring together what is already known about the role of PGx in making green drugs and targeted therapies. We used electronic databases such as PubMed, Scopus, Web of Science, and Google Scholar to look at the literature in a way that was not systematic but was still very thorough. The search terms were sets of keywords that had something to do with the topic. Some of them were "PGx," "personalized medicine," "sustainable drug development," "SNPs," "biomarkers," and "genetic variability in drug response." The data were thematically collated into the main areas of genetic variation in drug metabolism, bioinformatics resources, genome-wide screening, ethnic variation, clinical integration, and PGx innovations. It was very important to talk about both the scientific and translational problems that come up when trying to use PGx in medication development and clinical practice. The goal was to give a full but short description that points the way for future research in personalized and long-lasting medicine.

3. GENETIC VARIATION AND PHARMACODYNAMICS

3.1. Single-nucleotide polymorphisms

"Snips," or SNPs, are the most prevalent type of genetic difference between humans. A single base is modified at a certain spot in the DNA sequence, which causes it to happen. These mutations happen around once per 1,000 nucleotides. It is assumed that they are responsible for almost 90% of the differences in human DNA [5]. SNPs are helpful in genetic research because they enable scientists to uncover genes that are connected to particular traits and disorders. They are also important tools for constructing detailed maps of chromosomes [6]. SNPs are particularly essential for customized medicine since they change how people react to some medications. SNPs modify the amount and activity of transporters, receptors, and drug-metabolizing enzymes. This helps doctors pick the proper dose and type of medicine, improves the therapies work better, and minimizes the likelihood of harmful drug reactions [7]. Finding and describing SNPs is an important element of PGx that helps us learn how genes affect how well medications function and how bad they are for us. Many bioinformatics software tools have been built to help with sequence alignment, variant calling, and functional annotation so that SNPs may be found in large genomic datasets. Researchers in PGx used software such as Genome Analysis Toolkit (GATK), SAMtools, HaploSNPer, and BLAST, Since they are good at discovering SNPs that are relevant for medicine [8]. Figure 1 shows that these software applications are quite useful for detecting and studying SNPs. Adding these computer platforms makes it easier to find SNPs and lets doctors design treatment strategies that are unique to each patient. This helps with the goals of developing long-term medications and precision medicine.

3.2. Cytochrome P450 2D6 (CYP2D6)

CYP2D6 is among the most polymorphic enzymes in the cytochrome P450 superfamily, exhibiting significant interindividual variability that influences the metabolism of more than 50 therapeutically significant medications, including antidepressants, antipsychotics, β-blockers, and opioids [10]. Scientists have found more than 70 different forms of the CYP2D6 gene. Most of these forms cause the enzyme to work less well or not at all, which leads to different metabolizer phenotypes as follows: poor, intermediate, extensive, and ultra-rapid [11]. A lot has been written about this; however, right now the focus is on the long-term effects of CYP2D6 variability in clinical and pharmacological settings. When CYP2D6 polymorphisms are not recognized, they might lead to the wrong or too low dose of medication, which can cause more treatment failures, bad side effects, and wasted medication. These things put a strain on healthcare systems and make pharmaceutical pollution worse. Drugs that are not metabolized well may be excreted in their original form, which can get into wastewater systems and cause problems for the environment, especially with drugs that do not break down easily or last a long time [12]. Additionally, repeat prescriptions and polypharmacy that happen because of bad treatment plans add to unnecessary emissions from production, packaging, and the supply chain, which makes the pharmaceutical carbon footprint even worse. The polymorphic nature of CYP2D6 opens up new possibilities for sustainable clinical pharmacology: genotype-guided dosing reduces drug overuse, hospitalizations due to side effects, and environmental pollution from extra or unmetabolized drugs [13]. When applied to non-CYP2D6 drug-metabolizing enzymes, the effects are even stronger. These enzymes have more than 168 alleles, which lead to 97 functional protein changes. Adding CYP450 pharmacogenetic screening to standard care makes it possible to tailor treatment to each patient and supports therapeutic models that are ecologically friendly and use resources wisely. This paradigm sees CYP2D6 variability as a challenge to sustainability at the systems level, linking precision medicine with environmental stewardship and healthcare resilience [14].

3.3. Ethnic variations in drug response

Genetic polymorphisms are key to PGx, and they are the reason why patients and populations react variably to

a single drug. These differences usually vary in occurrence among ethnic groups and influence the pharmacokinetics and pharmacodynamics of many drugs. Figure 2 suggests inter-ethnic variations in frequencies of an allele for a PGx variant responsible for drug metabolism. Interestingly, the variant is more prevalent in African populations than in Asian and Caucasian populations, underlining the need for population-specific PGx screening. The genes that are linked to drug-metabolizing enzymes, transporters, and drug targets have different distributions in different populations. This affects how well the drugs work and how likely they are to cause adverse effects. There are more thiopurine methyltransferase variants that affect thiopurine metabolism in Caucasians than in Asians. However, there are more UGT1A1 polymorphisms that are linked to irinotecan toxicity in East Asians [15]. Agents like 5-fluorouracil (5-FU) and warfarin have variable responses based on such inherent genetic differences [16]. Identifying such ethnic-specific genetic patterns is crucial for putting PGx testing into practice and providing safe, effective, and targeted therapies.

3.4. Genotyping in developing countries

Genotyping is the technique of looking at a person's DNA sequence through biological studies to detect differences in their genetic makeup (genotype). Genotyping in medicine makes it possible to find genetic variations that affect how likely someone is to get sick, how well they process drugs, and how well they respond to treatment. Despite the promising advancements of PGx in personalized medicine, its implementation in developing countries is hindered by significant challenges. Inexpensive genotyping platforms, inadequate infrastructure, limited availability of skilled healthcare professionals, and deficient regulatory frameworks collectively hinder the use of these technologies [18]. Additionally, PGx recommendations are drawn from populations originating in high-income countries, contributing to the under-representation of multigenic African, Asian, and Latin American populations [19]. Discrepancies pose a problem with the translatability and significance of PGx data to clinical purposes within these geographies. Despite these limitations, initiatives such as the Human Heredity and Health in Africa (H3Africa) program have significantly advanced genomic capabilities and facilitated the establishment of

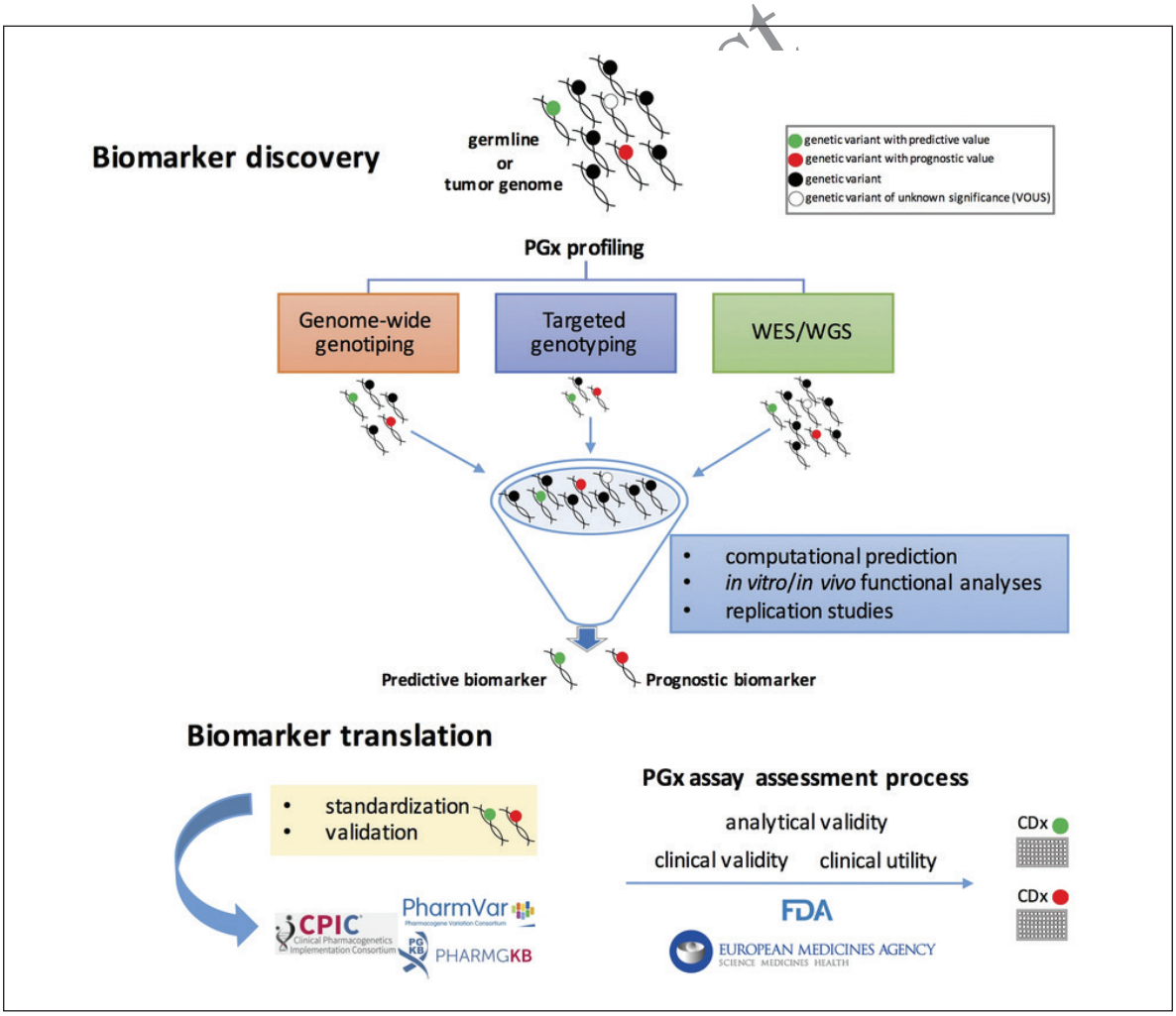

Figure 1. Bioinformatics tools for SNP detection in PGx [9]. Widely utilized platforms such as GATK, SAMtools, HaploSNPer, and BLAST facilitate sequence alignment, variant calling, and functional annotation.

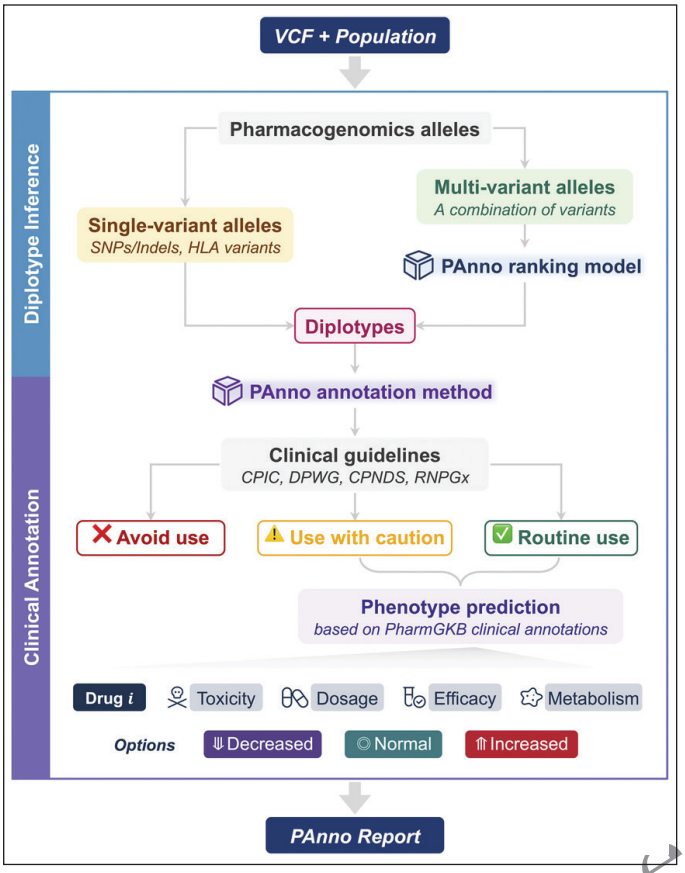

Figure 2. Ethnic variations in allele frequency of PGx marker [17]. Frequencies represent the approximate prevalence of a selected PGx variant relevant to drug metabolism.

population-specific genetic databases. These efforts are essential for the creation of localized clinical tools and the promotion of equity in genetic medicine [20]. To make sure that everyone can benefit from PGx, we need to keep investing in infrastructure, training, inexpensive technology, and research that includes everyone. Genotyping in poor countries is very hard because of high costs, a lack of lab infrastructure, a lack of experienced workers, and complicated logistics for managing and storing samples. If these issues are not addressed, they could make the global health equity gap even bigger. Still, practical and cost-effective options are becoming available. Frugal advances such as loop-mediated isothermal amplification combined with paper-based microfluidic devices show promise for low-cost, point-of-care genotyping that does not need a lot of fancy lab equipment. Reboud *et al.* [21] showed that this diagnostic platform could find *Plasmodium falciparum* DNA in blood samples taken from a finger prick in rural Ugandan schools in 50 minutes with 98% sensitivity, using just simple heating and optical detection equipment. H3Africa and other projects support the construction of regional genotyping hubs and continuous capacity-building initiatives. These are necessary to extend genotyping services while ensuring that local people own and are skilled in them. These models highlight that strategic innovation, training, and policy prioritization can make genomics feasible even in resource-constrained settings.

3.5. PGx approaches in drug discovery

Target discovery represents a pivotal process in drug development that entails the identification of genes, proteins, or molecular pathways pivotal for disease causation and progression. In PGx, it is reciprocally connected to deciphering genetic variance effects on disease susceptibility and treatment responses. By utilizing genome-wide association studies (GWAS), transcriptomic profiling, and integrative bioinformatics, scientists can detect new, population-associated molecular targets [22]. PGx simplifies drug discovery by providing genome-level information on variable drug responses, allowing pharmaceutical companies to design new therapeutics such as orphan drugs and enhance the efficacy of existing ones [23]. Genetically directed drug design makes drug development more accurate by letting drugs interact with some biological targets and reducing side effects on other targets. An excellent example is using mutations in the EGFR gene to help direct targeted therapy for non-small-cell lung cancer (NSCLC) [24]. In addition, PGx databases such as Pharmacogenomics Knowledge Base (PharmGKB) and databases such as the Drug-Gene Interaction Database (DGIdb) have aided in the connection of genetic variation with actionable targets for drugs [25]. This, in turn, not only favors the identification of the best target but also the prediction of biomarkers in support of deciding treatment. Combining multi-omics technology with clinical data makes it easier to find targets, which helps the development of safer and more effective personalized therapy, especially for complicated diseases such as cancer, diabetes, and heart disease. Ultimately, it helps the progress of precision medicine by reducing trial-and-error prescribing and bad drug reactions, while improving patient outcomes and lowering healthcare expenditures.

3.6. Environmental impact of PGx

PGx clearly makes long-term drug development better by reducing the consumption of resources and harm to the environment throughout the drug's life cycle. Unlike traditional techniques that only look at safety and effectiveness, PGx-guided prescribing cuts down on trial-and-error in therapy, which means that fewer medications are left over or thrown away and less pharmaceutical emissions come from hospitals [26]. Genotype-based precision dosing reduces the excretion of unmetabolized active pharmaceutical ingredients into wastewater, which is particularly critical for environmentally persistent compounds such as carbamazepine and diclofenac, associated with aquatic toxicity and antibiotic resistance [27]. In pharmaceutical manufacturing, PGx facilitates demand-driven synthesis by focusing on genetically stratified populations, hence preventing overproduction and minimizing energy use, raw material usage, and packaging waste. This lean manufacturing process follows the rules of green chemistry, which put a high value on reducing the use of harmful chemicals and solvents in the making of medicines [28,29]. PGx helps make narrow-spectrum, molecularly targeted medicines, which frequently means that the synthetic processes are faster and require less resources. This means that the medicines have a smaller chemical and carbon footprint. In clinical trials, PGx enhances enrichment algorithms that identify probable responders, thereby substantially reducing trial duration, drug waste, and

site-related emissions—an important advancement in mitigating the environmental impact of research and development [30]. As precision medicine progressively incorporates real-world data and AI-driven analytics, PGx is positioned to promote a low-waste, environmentally sustainable therapeutic model that links healthcare innovation with long-term planetary health objectives.

3.7. Emerging intersections supporting sustainability in PGx

PGx is quickly becoming part of new technologies and environmental changes that make drug development and treatment decisions more sustainable. AI-driven methods are changing the way biomarkers are found by making it possible to analyze a lot of genetic information quickly to predict how well a treatment will work and how harmful it will be. This means that fewer animals, chemicals, and expensive trial failures are needed in the early stages of development [31]. These computational models facilitate *in silico* simulations of drug–gene interactions, thereby reducing redundant laboratory experiments. Green chemistry, in conjunction with PGx data, enables the development of targeted drug delivery systems and synthetic pathways that diminish the use of hazardous substances and lower energy consumption in pharmaceutical production [32]. For example, smaller, more targeted batches of drugs that are meant for genetically receptive subgroups can be made, which cuts down on the amount of materials needed and waste. Real-world evidence (RWE) from large biobanks and electronic health records (EHRs) supports PGx findings across a wide range of patient groups, making them more reliable and helping doctors come up with better ways to prescribe drugs [33]. RWE makes it easier to keep track of PGx medicines once they are on the market, allowing researchers to see long-term effectiveness and population-specific trends in ADRs without having to undertake randomized trials over and over again. Combining PGx with transcriptomics, epigenomics, proteomics, and metabolomics into multi-omics makes it easier to classify patients and reduces the need for dose-finding studies [34]. By including real-world results in medication refinement, this systems-level accuracy cuts down on wasted resources, speeds up the introduction of new medicines to the market, and makes closed-loop pharmaceutical design easier. These discoveries in several fields support a lifecycle sustainability model in PGx that includes drug creation, clinical trials, therapeutic deployment, and outcome monitoring. PGx improves health outcomes by combining precision medicine with ecological and economic accountability. This makes healthcare systems more sustainable and resilient.

3.8. ADRs: novel PGx case studies

It is well known that certain PGx-ADR links, like HLA-B57:01 and abacavir hypersensitivity, exist. However, new cases are making PGx screening more important in the clinic. DPYD gene variations (e.g., DPYD 2A, 13, c.2846A>T) substantially increase the risk of severe fluoropyrimidine (5-FU, capecitabine) toxicity in cancer patients, necessitating compulsory pre-treatment genotyping in certain European nations [35]. In psychiatry, HLA-A31:01 has been identified as a predictor of carbamazepine-induced Stevens–Johnson syndrome in East and Southeast Asian populations, resulting in region-specific testing protocols [36]. Furthermore, polymorphisms in IL28B (e.g., rs12979860) are utilized to forecast prolonged virologic response in hepatitis C therapy with pegylated interferon and ribavirin, thereby minimizing unnecessary exposure to side effects in suboptimal responders [37]. These new associations demonstrate how PGx improves safety and promotes sustainable healthcare by reducing drug waste and hospitalizations.

3.9. Candidate gene approach

The candidate gene strategy includes the choice of genes with already known or suspected biological function in disease causation or drug effect, on the basis of prior knowledge of pathways. These genes are tested for association with a particular phenotypic characteristic or therapeutic response using either population studies or case-control contrasts. Such a strategy is especially useful when there is an established hypothesis of the role played by the gene in the disease case [38]. Contemporary molecular technology, such as genome-wide association studies (GWAS) and quantitative trait locus mapping, has improved the candidate-gene strategy by allowing high-throughput genetic variant screening of many candidates in large populations. These tools make it easier to find changes that cause diseases and to map out genomic areas that are connected to complicated traits. This gives us more information about how diseases work and what treatments might work [39]. The candidate gene strategy has been improved by combining *in silico* technology, pathway enrichment analysis, and DGIdb. This has made it possible to test fewer genes. For instance, the candidate genes unearthed from such PGx research, such as drugs metabolism, transport, or immune responses, have been significant factors in illuminating inter-individual variability of drugs' effects as well as drug side effects [40]. In the pursuit to develop precision medicine, however, the candidate gene strategy will continue being a vital approach used in applying genome knowledge in to clinical uses and especially with supplementary large-scale omics information coupled with functional data.

3.10. Genome-wide screening

Genome-wide screening is a useful method for finding genes or genetic differences that are linked to certain traits, diseases, or phenotypes. High-throughput screening (HTS) technologies have made a big difference in this field by making it possible to quickly and fairly look at gene functions across the full genome [40]. HTS has made whole-genome sequencing possible, which lets scientists look at an organism's entire genetic code in detail. This gives them important information about how complex biological systems work [41]. There are five main steps in the full HTS process: collecting samples, extracting DNA/RNA, preparing the library, sequencing, and interpreting the findings (Fig. 3). The procedures guarantee the identification of genetic variations with high-resolution precision. Among novel HTS methodologies, CRISPR-based screening has evolved into a reliable and effective technology. The CRISPR-associated protein 9 (Cas9), guided by specific RNA sequences, enables accurate targeting and modification of

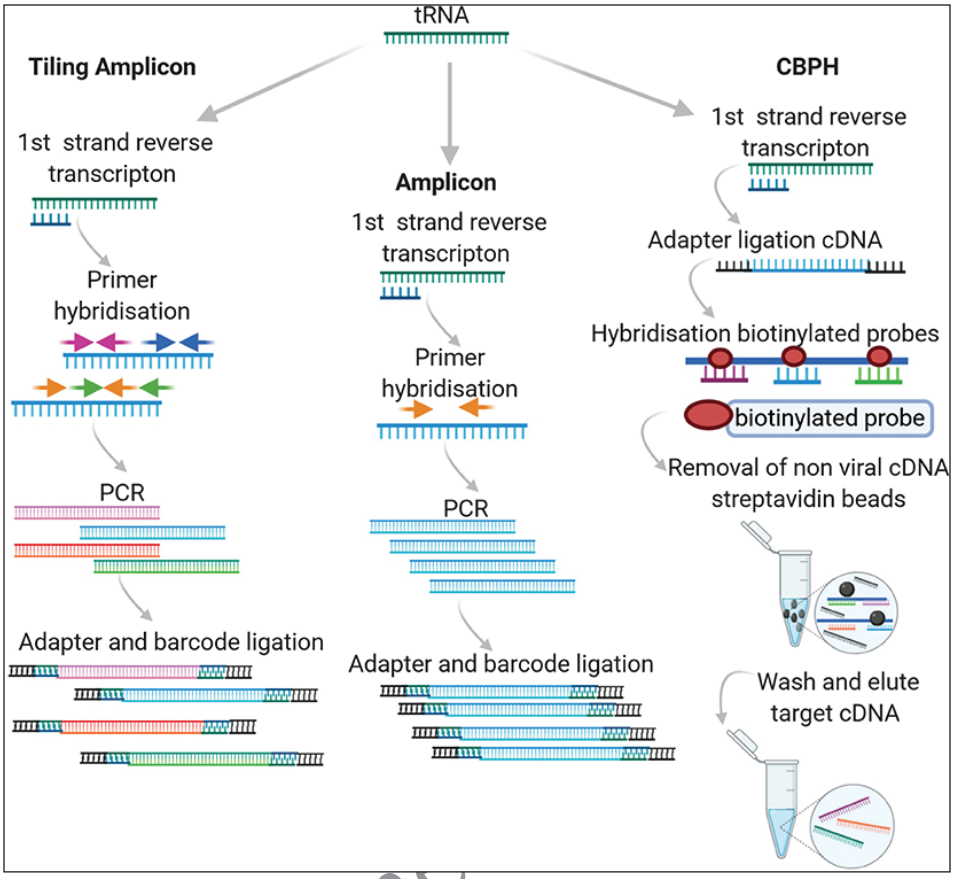

Figure 3. Workflow of HTS [45]. The procedure comprises sample collection, DNA/RNA extraction, library preparation, sequencing, and bioinformatics analysis, utilized for genome-wide variation finding.

DNA regions. It has been very important in functional genomics because it lets scientists study gene functions and interactions across the whole genome in a systematic way [43]. CRISPR genome-wide screens have also been very good at finding genes that are involved in disease processes, especially in the formation of cancer and the replication of viruses. This has led to new techniques to treat these diseases [44]. The utilization of advanced genome-wide screening tools has revolutionized genetic research, facilitating the development of customized treatment and enhancing our understanding of the genetic underpinnings of numerous disorders.

4. PHARMACOGENETICS IN CLINICAL APPLICATION

4.1. Pharmacogenetics: implications in clinical practice

Pharmacogenetics offers an essential understanding of individual differences in medication response, allowing doctors to enhance efficacy and minimize ADRs. Immune-mediated ADRs, which can be life-threatening, are often linked to mutations in the HLA gene complex [46]. HLA-B15:02 is significantly associated with carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis in Southeast Asian populations [47], whereas HLA-B57:01 is a recognized predictor of abacavir hypersensitivity [48]. Global directives, including those from the Clinical Pharmacogenetics Implementation Consortium (CPIC), now offer actionable gene-drug recommendations [49]; however, clinical implementation is inconsistent due to obstacles such as inadequate clinician training, absence of reimbursement frameworks, and insufficient representation of diverse populations in genomic research [50–52]. Pharmacogenetics has more potential for healthcare and environmental sustainability than just improving clinical results. PGx-guided therapy helps reduce unnecessary hospital stays, intensive care unit admissions, and repeated treatments by finding those who are more likely to have severe drug reactions, like HLA-associated hypersensitivity. All of these things have a big impact on resources and carbon footprints. Reducing severe drug responses reduces the need for emergency pharmacological treatments and the waste that comes with them, such as unused medicines and hazardous disposal. Additionally, tailored screening methods for certain populations (such as HLA testing in areas with a high prevalence of alleles) can help distribute medicine in the most effective way, which can help prevent overstocking and product expiration. Adding pharmacogenetic information to EHRs makes healthcare more sustainable in the long term by reducing needless diagnoses, making it easier to customize therapy over time, and lowering the environmental effect of fragmented care. These points of view show that pharmacogenetics is an important part of precision medicine and a way to make healthcare systems more sustainable and use less resources.

4.2. Genetic variation in drug transport

Genetic diversity in drug transport proteins is of great relevance in the regulation of differential responses to pharmacologic agents. Transporters such as those belonging to the ATP-binding cassette and solute carrier superfamilies mediate the uptake and efflux of a broad spectrum of drugs across cell membranes. Genetic polymorphisms within coding genes of such transporters have the ability to significantly impact drug absorption, distribution, and elimination and consequently drug efficacy and risk of toxicity [53]. One such well-known example is polymorphisms in ABCB1 (P-glycoprotein), which have been shown to affect drug efflux in organs like the intestines, liver, kidney, and brain. These polymorphisms are the cause of altered bioavailability of chemotherapeutic drugs, antivirals, and cardiovascular drugs, influencing both therapeutic action and ADRs [54]. Similarly, polymorphisms in SLCO1B1, the gene encoding the hepatic uptake transporter OATP1B1, have been linked to statin-induced myopathy due to reduced hepatic clearance [55]. Understanding these genetic variations in PGx is important because they form the basis of the development of personalized drug regimens aimed at maximizing efficacy with minimized side effects.

4.3. Genetic variation in drug targets

Genetic polymorphisms in drug target genes such as enzymes, receptors, or ion channels may have a significant impact on drug efficacy and safety. These polymorphisms can affect the binding affinity, functional activity, or expression levels of target proteins and result in interindividual variability in therapeutic response [56]. For instance, epidermal growth factor receptor (EGFR) alterations have been associated with heterogeneous sensitivity to tyrosine kinase inhibitors in non-small-cell lung carcinoma, emphasizing the need for genetic screening prior to therapy [57]. Therefore, such variations are particularly relevant in chronic and multifactorial conditions such as cancer, where targeted therapy is determined by the genetic composition of the tumor or by the host. Adding PGx testing to assess target-related polymorphisms allows for more accurate prediction of treatment efficacy and allows precision medicine to be developed.

4.4. PGx of chemotherapy toxicity

Clinical application of chemotherapeutic drugs is often limited by their high toxicity profiles, excluding classical genetic investigation in healthy humans. In addition, drug toxicity and therapeutic effect are multifactorial traits often determined by multiple genetic loci, and hence, it becomes challenging to identify a single genetic marker with significant genome-wide importance [58]. PGx research has still identified the most important genetic variations affecting drug metabolism and toxicity. A notable case is dihydropyrimidine dehydrogenase, the protein coded for by the DPYD gene, which is essential for the metabolism of 5-FU and capecitabine. DPYD polymorphism deficiencies have also been associated with severe, and occasionally life-threatening, toxicity in individuals receiving fluoropyrimidine-based treatment [59]. To enable clinical translation of such evidence, tools such as the PharmGKB aggregate gene–drug interaction information, and the CPIC provides actionable recommendations for incorporating genetic testing into standard patient care [60]. These platforms provide customized treatment protocols that minimize side effects and improve therapeutic efficacy.

5. GENOMICS AND EPIGENOMICS IN PGX

5.1. Epigenomics and clinical applications in PGx

Epigenomics investigates inheritable modifications in gene expression that occur without changes to the fundamental DNA sequence, including DNA methylation, histone modification, and regulation by non-coding RNA. Traditional genomics tells us about the existence of genes and polymorphisms, while epigenomic markers give us real-time knowledge about how genes are expressed in different health and disease states. More and more, epigenetic changes are being seen as useful for predicting how well a medicine will work in a therapeutic environment. DNA hypermethylation of the MGMT gene promoter is linked to a better response to temozolomide in glioblastoma patients, which makes tiered therapy possible [61]. In the same way, DNMT3A mutations and patterns of hypomethylation are linked to bad outcomes and resistance to treatment in acute myeloid leukemia [62]. In breast cancer, the epigenetic silencing of ERα predicts resistance to tamoxifen, affecting therapy choices. Pharmacological regulation of the epigenome has emerged as a therapeutic method, as demonstrated by FDA-approved epigenetic agents such as vorinostat and azacitidine, which are histone deacetylase (HDAC) and DNA methyltransferase inhibitors, respectively [63]. These medicines are utilized in hematologic malignancies and are being assessed in conjunction with immunotherapy and chemotherapy to surmount resistance and enhance efficacy. The incorporation of epigenomic profiling in PGx extends personalized medicine to include dynamic and reversible regulators of gene function, offering a more comprehensive prediction of drug response and resistance mechanisms. In Alzheimer's disease, histone modifications and non-coding RNAs influence neuronal gene expression and may serve as biomarkers or therapeutic targets. Moreover, prenatal epigenetic screening is emerging as a tool to assess fetal health and predict future disease risk, supporting early intervention strategies.

5.2. Acquired genomic variations and their role in personalized drug response

Acquired genomic variations, or somatic mutations, occur in a person's lifetime as a result of environmental exposures, lifestyle, or DNA replication errors. In contrast to inherited mutations, these variations are present in individual cells and are not inherited by offspring. In PGx, acquired genomic changes can significantly influence a person's drug metabolism, drug response, and ADRs [64]. For example, mutations in somatic drug-metabolizing enzymes such as CYP450 are known to vary the patient's rate of metabolism of a drug, determining therapy outcomes [65]. This justifies studying gained genetic modifications as part of establishing personalized medicines. In diseases like cancer, acquired mutations significantly contribute

Table 1. Comparison of genomics and epigenomics in PGx.

Parameter	Genomics	Epigenomics	Clinical application
Emphasis	Inherited DNA sequence variations.	Chemical modifications regulating gene expression.	Epigenetic changes help identify therapy-sensitive and -resistant subtypes across cancers (e.g., MGMT methylation in glioblastoma).
DNA structure	Analyses DNA sequence, structure, and mutations.	Modifies gene activity without altering DNA sequence.	Epigenetic profiling adds functional layers to genomic analysis for improved drug response prediction.
Key processes	Gene identification, mutation analysis, and mapping.	DNA methylation, histone modification, and chromatin remodeling.	Targets for epigenetic therapies (e.g., HDAC and DNMT inhibitors such as vorinostat and azacitidine).
Environmental factors	Minimal influence from environmental factors.	Strongly influenced by lifestyle, diet, and external conditions.	Lifestyle-related epigenetic changes may serve as early indicators of disease or drug responsiveness.
Reversibility	Mutations are permanent and fixed.	Epigenetic modifications are often reversible and dynamic.	Enables pharmacological intervention (e.g., reversing resistance by reactivating silenced genes).
Applications	Genetic disorder understanding, trait analysis, and evolution.	Insights into gene regulation, development, and disease mechanisms.	Stratification of patients for tailored therapy, monitoring treatment response, and guiding combination therapies in oncology and beyond.

to tumor heterogeneity, thereby impacting the response of tumors to various treatments. Specific mutations may result in resistance of cancer cells against certain therapies or may make a drug more potent. These changes are critical to the development of treatment plans and can be assessed by genetic profiling of acquired mutations to identify those patients who might benefit more from targeted therapies or immunotherapy. Integrating inherited genomic variation into PGx designs enables better drug development through increased accuracy of drug efficacy prospects while reducing chances of adverse reactions, especially within personalized medicine methodologies (Table 1) [66].

6. ROLE OF BIOMARKERS IN THERAPY

6.1. Molecular markers guiding drug therapy

Molecular markers are critical tools in the direction of drug therapy, with examples being predictive, therapeutic, and pharmacodynamic biomarkers. Predictive biomarkers determine individuals who are likely to benefit from a given treatment, whereas therapeutic biomarkers determine if the drug has successfully targeted the disease. Advances in molecular imaging technologies have greatly enhanced therapeutic monitoring, allowing real-time evaluation of drug action. Some of these include radiopharmaceuticals, through which therapies like those for neuroendocrine tumors can be tracked [68]. Further, quantitative molecular imaging methods, such as the utilization of ^{89}Zr-oxine (zirconium-89 oxine) for live drug tracking, allow accurate drug dosing and therapeutic response measurement [67]. The development of molecular diagnostic technologies such as DNA chip technology, capillary electrophoresis, MALDI-TOF mass spectrometry, and real-time polymer chain reaction has enabled one to evaluate biomarkers for individualized therapy more effectively. These technologies enable more precise evaluation of individual genetic profiles so that drugs can be administered with a greater chance of efficacy and fewer side effects. Robot systems also complement these diagnostics by supporting HTS and meticulous analysis of molecular markers [69].

7. RISK AND RESPONSE ASSESSMENT

7.1. Disease risk studies in PGx

Disease risk research is at the core of the identification of genetically susceptible individuals and the development of personalized therapeutic approaches. SNPs and clinical factors like smoking status, age, and lipid levels are commonly employed to forecast disease susceptibility. These models facilitate early intervention approaches and enable the accurate targeting of pharmacological interventions according to genetic risk [70]. In PGx, these tools assist in stratifying patients based on their risk profiles to enhance drug efficacy and safety. Disease Risk Score (DRS), a statistical tool designed to measure individual risk according to genetic and environmental variables, has gained popularity among epidemiological and therapeutic outcome research. In contrast to propensity score, DRS may be applied in scenarios where treatment allocation is affected by anticipated disease risk, providing a powerful method of confounding adjustment [71]. As part of personalized medicine, DRS facilitates improved therapeutic targeting, particularly for complicated, multifactorial disorders like cardiovascular diseases and diabetes [72]. Integrating these risk assessments within PGx platforms ensures drug development that is sustainable through better resource allocation and patient-tailored therapy.

7.2. Disease therapy response studies

Disease therapy response studies assess how patients react to specific treatments, helping to optimize therapeutic strategies and personalize medicine. These studies identify how genetic, molecular, and environmental factors influence the effectiveness and side effects of treatments, guiding clinicians in selecting the most suitable therapies for individual patients. For example, in NSCLC, PD-L1 expression on tumor cells predicts the efficacy of pembrolizumab, an immune checkpoint inhibitor [73] demonstrated that patients with PD-L1 expression ≥50% had significantly better progression-free survival when treated with pembrolizumab compared to chemotherapy. PGx further enhances therapy response by tailoring drugs based on genetic

profiles, minimizing side effects, and improving efficacy. For example, *CYP2C19* genetic variations affect the metabolism of clopidogrel, influencing cardiovascular treatment outcomes, with reduced-function alleles leading to less effective platelet inhibition [74]. These studies play a crucial role in advancing personalized medicine and sustainable drug development. While *CYP2C19* polymorphisms remain clinically relevant, recent studies highlight the limitations of single-gene testing and advocate for more comprehensive approaches. Polygenic risk scores (PRS), which aggregate the effects of multiple genetic variants, offer improved predictive power for cardiovascular events and drug responsiveness. Khera *et al.* [74] demonstrated that PRS can stratify coronary artery disease risk more effectively than traditional risk factors alone, supporting their utility in guiding antiplatelet. Furthermore, multi-omics integration, combining genomics, transcriptomics, proteomics, metabolomics, and epigenomics, is reshaping precision cardiology. Xie *et al.* [75] illustrated that layered omics data can uncover biological networks linked to clopidogrel resistance, facilitating personalized antiplatelet strategies. Similarly, Hasan *et al.* [76] reported that integrating transcriptomic and metabolomic signatures improved the prediction of platelet reactivity beyond *CYP2C19* genotyping alone in post-PCI patients. These emerging frameworks support a shift from monogenic pharmacogenetics to network-based, systems pharmacology, allowing for more accurate risk stratification, treatment optimization, and prediction of adverse events in cardiovascular care.

7.3. Microbiome- PGx

Pharmacomicrobiomics, digital health integration such as embedding PGx within EHRs, and health-economic evaluation of PGx are critical yet often overlooked components in implementing PGx in resource-limited settings. The gut microbiome profoundly influences drug metabolism, efficacy, and toxicity—for instance, microbial β-glucuronidase can reactivate irinotecan causing gastrointestinal toxicity, and gut bacteria may inactivate drugs like digoxin or activate pro-drugs such as lovastatin—highlighting the necessity to integrate microbiome–drug interaction data into PGx frameworks Simultaneously, integrating PGx data into EHRs via HL7 FHIR-based genomic indicators and clinical decision support systems (e.g., implementations in Epic's Genomic Module) has demonstrated improved clinician uptake, reduced manual data handling, and enhanced prescribing accuracy. Finally, systematic reviews in low- and middle-income countries indicate that single-gene PGx testing—especially when targeted at high-impact drugs for cancer, cardiovascular disease, or epilepsy—is frequently cost-effective and often cost-saving, with outcomes contingent on allele prevalence and test pricing [78]. These strategies together emphasize that addressing microbiome influences, enabling seamless EHR integration, and conducting rigorous economic evaluation are essential to truly realize the benefits of PGx in settings constrained by resources [79].

8. PERSONALIZED AND PRECISION MEDICINE

8.1. Pharmacogenetics in clinical practice

Pharmacogenetics is the research on how genetic differences influence drug responses in individuals, allowing for more tailored, effective, and safer treatment options. Through the identification of genetic markers that impact drug metabolism, effectiveness, and side effects, pharmacogenetics optimizes therapeutic outcomes. For instance, patients with the HLA-B1502 allele are at increased risk for serious skin reactions to carbamazepine, especially among Asian populations [80]. The SLCO1B1 gene mutation can predispose to statin-induced myopathy, informing the choice of statin [81]. Moreover, genetic assessment for HER2 overexpression defines the effectiveness of trastuzumab in HER2-positive breast cancer [82]. These are instances where pharmacogenetic testing is used to tailor drug treatment to the individual, maximizing effectiveness and reducing side effects.

8.2. Cancer pharmacogenetics and PGx

Cancer pharmacogenetics and PGx are interested in how genetic differences affect cancer treatment outcomes so that personalized therapies can be applied. Pharmacogenetics examines individual gene variants affecting drug metabolism and efficacy, for example, the DPYD gene, which impacts fluoropyrimidine metabolism like 5-FU, with testing enabling the prediction of risks of toxicity [83]. Additionally, CYP2D6 polymorphisms determine tamoxifen effectiveness in the treatment of breast cancer, with some reducing the efficacy of drugs [84]. On the contrary, PGx scans the whole genome to comprehend intricate genetic interactions with drug responses. For instance, EGFR mutations have resulted in the development of targeted therapies such as erlotinib for the treatment of NSCLC [85]. Both areas empower doctors to formulate cancer treatments for individual genetic signatures, maximizing drugs' effectiveness while reducing side effects.

8.3. Personalized precision medicine

Personalized precision medicine is a term used for adapting medical care to the specific features of an individual patient by using genetic, epigenetic, environmental, and lifestyle information to inform therapy. In the field of PGx, this practice facilitates the use of drugs and drug doses that produce the highest benefits with the fewest adverse effects according to a person's genotype. Major advances in high-throughput sequencing (HTS) and bioinformatics have led to the facilitation of inclusion of genomic data in clinical applications, enabling the discovery of pharmacogenetic variants that affect drug efficacy, metabolism, and toxicity [86]. This precision strategy has resulted in advances in the treatment of cancers, cardiovascular diseases, and metabolic disorders through a matching of therapeutic approaches with biomarker-guided profiles. For example, targeted therapies such as ivacaftor for cystic fibrosis are evidence of the efficacy of genomics-based treatments [87]. In addition, the integration of machine learning into PGx is improving predictive modeling of drug response, thus ensuring an improved, sustainable, and efficient drug development.

8.4. Human Genome Project (HGP) in PGx

The HGP, achieved in 2003, set a revolutionary stage for PGx by sequencing the entire human genome and making possible the identification of genetic variants affecting drug response. This pioneering project made it possible to identify gene-

drug interactions with critical pharmacogenes such as CYP2C9, CYP2D6, and SLCO1B1, which are critical in establishing drug metabolism, transport, and toxicity [88]. Recent progress has followed HGP findings in incorporating genomic data into everyday clinical care. More efficient sequencing technologies and population-scale genomic libraries are increasingly applied to stratify patients according to PGx characteristics, informing individualized therapy and reducing toxicities [89]. In addition, the post-HGP era has witnessed the creation of clinical PGx guidelines and decision-support tools that associate genetic variants with dosing recommendations, thus fueling sustainable and precision-driven drug development [90].

9. LIMITATIONS AND TECHNICAL CHALLENGES

One of the primary challenges in PGx studies is the correct identification and interpretation of rare and de novo genetic variants, which tend to lie beyond the purview of standard reference genomes and population datasets [91]. These variants have the potential to affect drug metabolism and response but are often overlooked or misclassified because of shallow coverage or sequencing depth. Identifying genuine functional variants from sequencing artifacts is still another important challenge, demanding high-fidelity validation platforms and bioinformatics pipelines, which are time-consuming and expensive [92]. In addition, population diversity creates a major barrier, as many available PGx datasets are disproportionately drawn from people of European ancestry. This bias is responsible for lowered predictive accuracy and clinical utility for underrepresented populations, thus threatening equal access to personalized medicine [93]. Ethical issues involving privacy, data sharing, and informed consent also make integrating PGx data into practice challenging. It is important to overcome these technical, ethical, and demographic obstacles in order to develop sustainable and inclusive PGx-based medicines.

10. ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS (ELSI) IN PGX

Implementation of PGx in the clinical setting presents significant **ELSI** that should be appropriately evaluated to allow for responsible and equitable healthcare provision.

10.1. Patient privacy and data protection

PGx data carry significant privacy risks due to their potential to reveal information about an individual's health, ancestry, and predisposition to disease. As these data are increasingly integrated into EHRs and large-scale biobanks, robust data protection mechanisms are essential. Re-identification risks persist even with de-identified datasets, particularly in the era of AI-driven analytics [94]. Compliance with regulations such as the General Data Protection Regulation in Europe and the Health Insurance Portability and Accountability Act in the United States is critical to maintaining confidentiality and data integrity. However, inconsistent international standards complicate data sharing and hinder global PGx collaborations [95]. Emerging frameworks advocate for dynamic consent models, tiered access controls, and blockchain-based audit trails to empower participants and enhance transparency [96]. Prioritizing patient-centric governance ensures ethical data use while enabling scientific and clinical advancements in PGx.

10.2. Equity in access to genetic testing

PGx testing remains largely inaccessible in many low- and middle-income countries due to high costs, insufficient infrastructure, and lack of trained personnel. These disparities limit the global applicability of personalized medicine and may widen existing health inequalities [97]. Furthermore, the underrepresentation of diverse populations in genomic databases can reduce the clinical validity of PGx tools across different ethnic groups [98]. Ensuring equitable access requires targeted investments in local infrastructure, education, and research inclusion policies [99].

10.3. Ethical dilemmas in gene editing and AI-driven medicine

Rising technologies like CRISPR-Cas9 and artificial intelligence (AI) in PGx create novel ethical problems. Gene editing, particularly of the germline, invites concern regarding unwanted outcomes, late impacts, and moral permissibility of editing inheritable features [100]. In the same manner, applications of AI within PGx decision-making require a careful approach so as to eschew algorithmic prejudice, loss of explainability, and diminished patient control [101]. Regulatory frameworks must evolve to ensure these technologies are developed and applied ethically, emphasizing oversight, fairness, and informed consent.

11. FUTURE PROSPECTS IN PGX INNOVATION

The destiny of PGx is set to be revolutionized by new technologies such as real-time nanopore sequencing and AI data analytics. These are making it possible to quickly, economically, and precisely detect SNPs and other genomic variations, thereby driving the adoption of personalized drug development approaches [102]. Nanopore sequencing, for example, enables real-time analysis with minimal sample preparation and has practical benefits in both clinical and research environments [103]. CRISPR systems are transforming functional genomics by providing accurate editing and verification of gene variants, enabling scientists to determine their involvement in drug response and disease advancement [104]. The tools, combined with diminishing costs of sequencing and the increased availability of genetic platforms, are likely to make personalized pharmacotherapy more accessible to larger populations. Finally, such breakthroughs are to cause a paradigm shift towards predictive, preventive, and participatory healthcare, enhancing therapeutic efficacy and reducing side effects.

12. CONCLUSION

PGx represents a well-established strategy for optimizing therapy by tailoring drug selection and dosing based on individual genetic variation. By incorporating genomic, epigenomic, and molecular information, PGx enhances the predictability of drug efficacy and significantly reduces the risk of ADRs. This precision improves patient safety and therapeutic consistency across varied clinical contexts. Additionally, PGx has demonstrated benefits in reducing unnecessary drug use and

minimizing treatment failures, contributing to more efficient healthcare delivery. Despite these gains, challenges such as limited population diversity in genetic databases and variability in clinical implementation remain areas of ongoing research. Nevertheless, the ability of PGx to improve drug response and safety profiles has been well documented across oncology, cardiology, psychiatry, and infectious disease therapeutics. These established advantages position PGx as a valuable tool for achieving more effective, patient-centered care in modern clinical practice.

13. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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This study does not involve experiments on animals or human subjects.

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All data generated and analyzed are included in this research article.

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19. USE OF AI-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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